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Predicting red blood cell transfusions in very low birth weight infants based on clinical risk factors.

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Predicting Red Blood Cell Transfusions in Very Low Birth Weight Infants Based on Clinical Risk Factors

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ABSTRACT

Objective: to describe the clinical factors most predictive of red blood cell transfusion in very low birth weight (VLBW) infants.
Study design: retrospective review of VLBW infants cared for at a single level III NICU during a two year period, n=199.
Results: overall transfusion requirement was 4.6 ± 6.2 transfusions/infant/hospital course. Length of hospital stay, days of mechanical ventilation, requirement for dopamine support, birth weight, initial hematocrit, periventricular leukomalacia and necrotizing enterocolitis all independently correlated with number of transfusions and donors. Bronchopulmonary dysplasia and patent ductus arteriosus were associated with donor but not transfusion number.
Conclusions: our data characterize the population of VLBW infants with the greatest blood transfusion and donor requirement. Further investigation is needed to target this population for interventions to reduce blood exposure.

Anemia of prematurity with the subsequent need to transfuse red blood cells (RBC) is a common problem in preterm infants. The most promising intervention to reduce the number of RBC transfusions in preterm infants has been the use of recombinant human erythropoietin which has been shown to safely stimulate erythropoiesis and decrease the requirement for transfusions in selected preterm infants.[1-3] Other interventions such as transfusion of placental blood,[4] and changing the preservative of red blood cells to allow transfusion of older blood[5] have also been suggested in order to decrease postnatal donor exposure but have not been extensively investigated in studies involving large numbers of infants. To date, the sub-population of preterm infants who would most likely benefit from these new therapies has been poorly defined. The purpose of this study was to: 1) determine which preterm infants require the most transfusions of RBC and have the greatest donor exposure and 2) establish the population of infants that would potentially derive the greatest benefit from interventions to limit exposure to blood products. In order to meet these goals we retrospectively created multivariate linear regression models to determine the clinical variables determining both RBC transfusion and donor number.

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METHODS

The study consisted of a retrospective review of infants admitted to the intensive care nursery at the Medical Center of Delaware from July 1, 1993 to July 1, 1995. The Medical Center of Delaware is a level III neonatal intensive care unit caring for both inborn and outborn infants. All data were obtained from a review of a computerized database and confirmed by chart review. Infants were included in the analysis if they had a birth weight less than 1500 grams and were offered intensive care. In order to establish the relationship of blood transfusion with intraventricular hemorrhage and bronchopulmonary dysplasia, infants were only included if they met the above criteria, had a minimum of one cranial sonogram, and survived to 28 days of life, n=199. Infants not analyzed included: 22 infants who were admitted and transfused but died prior to 28 days of life, and two infants (1380 grams and 1490 grams) not transfused who did not receive a cranial sonogram at the discretion of the attending neonatologist.

For the purpose of this study, a blood transfusion was considered the administration of packed red blood cells as ordered by the attending neonatologist. All transfused blood is negative for cytomegalovirus, irradiated, less than seven days old and stored in citrate-phosphate-dextrose-adenine preservative. Blood from a single donor, which was ordered to be split into multiple smaller aliquots, and transfused within 24 hours, was considered a single transfusion. If an infant received a second transfusion > 24 hours following an original transfusion, but before the seven day expiration period of the blood, the transfusion was considered a second transfusion but a single donor exposure. Therefore infants often receive multiple transfusions from a single donor. All transfusions ordered after the seven day expiration period of the original unit were from a different donor.

The following general criteria are adhered to in our nursery: most transfusions ranged from ten to 15 cc/kg per transfusion. During the acute phase of respiratory distress syndrome, infants are transfused to keep the hematocrit greater than 35-40 percent. Anemic preterm infants who are more stable and receiving enteral feeds and no supplemental oxygen were transfused only if they are felt to be symptomatic. These symptoms included: tachycardia, tachypnea, poor weight gain while receiving adequate calories, and frequent apnea unresponsive to other therapies.

The independent variables studied are listed (Table 1). For the purpose of this study gestational age was defined by the best obstetrical estimate or if not available by Ballard exam.[6] Patients were given the diagnosis of bacterial sepsis if they had a positive blood culture and the diagnosis of patent ductus arteriosus if confirmed by echocardiography. Bronchopulmonary dysplasia was defined as a requirement for supplemental oxygen at 28 days of life.[7] Prolonged rupture of membranes was defined as being greater than 24 hours in duration. Premature rupture of membranes was defined as rupture before 37 weeks of gestation.

Multivariate linear regression models were created in order to determine which clinical factors were most predictive of the number of transfusions and the number of donors. Number of red blood cell transfusions and number of donors served as the dependent variables. Independent variables entered in the models were determined by performing a preliminary univariate analysis as well as multiple linear regressions. Forward stepwise analysis was performed in order to determine variables independently associated with transfusion and donor number. Validity of the models was confirmed by plotting residuals versus expected normal values and residuals versus predicted values. All data are expressed as mean ± standard deviation, unless otherwise noted. All statistical calculations were performed on commercially available software (Statistica, Tulsa, OK).

Table 1. Independent variables studied in multivariate models. Dependent variables, transfusion number and donor number.

INDEPENDENT VARIABLES STUDIED
Gestational Age
Birth Weight
Intrauterine Growth Restriction
Length of Hospital Stay
Gender
Mechanical Ventilation
High Frequency Ventilation
Days of Mechanical Ventilation
Continuous Positive Airway Pressure
Days of Continuous Positive Airway Pressure
Days of Supplemental Oxygen
Prenatal Steroids
Exogenous Surfactant
Apnea of Prematurity
Caffeine
Dopamine
Dobutamine
Initial Hematocrit
Patent Ductus Arteriosus
Bacterial Sepsis
Intraventricular Hemorrhage
Severe Intraventricular Hemorrhage, grade III-IV
Periventricular Leukomalacia
Necrotizing Enterocolitis
Bronchopulmonary Dysplasia
Seizures
Pneumothorax
Mortality
Preeclampsia
Premature Labor
Maternal Substance Abuse
Multiple Gestation
Prolonged Rupture of Membranes
Premature Rupture of Membranes
Maternal Urinary Tract Infection
Chorioamnionitis
Oligohydramnios
Maternal Age
Number of Platelet Transfusions
Prenatal magnesium sulfate

RESULTS

The overall requirement for transfusions of RBC was 4.6 ± 6.2 per infant/hospital course (range 0-40). Thirty-five percent of the study population did not require any RBC transfusions throughout their hospital course, while five percent required only a single transfusion, 13 percent required two to three RBC transfusions, 12 percent required four to five RBC transfusions and the remaining 35 percent required six or more transfusions. The mean number of donors was 2.6 ± 3.1 per infant / hospital course (range 0 -17). Thirty-five percent had no donor exposures, while ten percent had a single exposure, 20 percent had two to three exposures, 18 percent had four to five exposures, and the remaining 17 percent had six or more RBC donors. None of the infants in the study received recombinant erythropoietin. The demographic makeup of the study population is listed in Table 2.

Variables independently correlating with number of RBC transfusions included: length of hospital stay ($p<.00001$), number of days of mechanical ventilation ($p < .0001$), requirement for dopamine support ($p< .00001$), diagnoses of periventricular leukomalacia ($p=.00004$) and necrotizing enterocolitis ($p= .002$), birth weight ($p=.002$), and initial hematocrit ($p=.04$). The overall model had an $r=0.9$ ($p<.001$). None of the other variables studied (Table 1) correlated with number of transfusions.

Variables associated with number of donors included: length of hospital stay ($p<.00001$), number of days of mechanical ventilation ($p < .00001$), requirement for dopamine support ($p< .00001$), diagnoses of bronchopulmonary dysplasia ($p=.0004$) and periventricular leukomalacia ($p=.01$), birth weight ($p=.03$), initial hematocrit ($p=.03$) and diagnoses of necrotizing enterocolitis ($p= .03$) and patent ductus arteriosus ($p=.04$). The overall model had an $r=0.91$ ($p<.00001$). None of the other variables studied (Table 1) were associated with number of donors.

Because most of the variables correlating with number of transfusions and number of donors in the above models are not known until later in an infant's hospital course, an attempt was made to create a model using variables available at the time of birth. Using only birth weight and initial hematocrit as the independent variables and transfusion number as the dependent variable had an r =.71 ($p<.001$). Using donor number as the dependent variable with the same independent variables had an r=.69 ($p<.001$).

DISCUSSION

The etiology of the anemia of prematurity is multifactorial. The pathophysiology results from an attenuated erythropoietin response to tissue hypoxia, [8] iatrogenic blood loss, [9,10] and shortened life span of RBC containing fetal hemoglobin. [9] Although the risk of HIV infection from random donor blood is one in 450,000 to one in 600,000 in the United States, [11] transfusion of blood products is associated with significant parental anxiety. Other risks from exposure to blood products include: hepatitis B and C, as well as volume overload, electrolyte disturbances, iron overload and graft versus host disease.[12] These risks highlight the importance of developing methods to decrease transfusion and donor number in this population. Our data demonstrate that length of hospital stay, days of mechanical ventilation and need for dopamine support are the variables most predictive of number of transfusions and donors. Birth weight, initial hematocrit, periventricular leukomalacia and necrotizing enterocolitis are also independent predictors of transfusion and donor number. Diagnosis of patent ductus arteriosus and bronchopulmonary dysplasia are related to donor number but not transfusion number.

To our knowledge this report is the first to correlate length of hospital stay with transfusion and donor number. We speculate that infants with prolonged length of stay had increased phlebotomy losses. Obladen et al have previously demonstrated that infants of lower birth weight and infants who require respiratory support have increased blood sampling. [10] Phlebotomy data was not included in this investigation because it was not uniformly available in our population. Number of transfusions and donors may also be related to length of stay because of a prolonged opportunity to transfuse infants, as the hematocrit of infants discharged to home is generally unknown to the attending physician.

Table 2. Demographic make-up of the study population.

DEMOGRAPHIC DATA (n=199)	
Birth Weight (grams)	1089 ± 279*
Gestational Age (weeks)	28.5 ± 2.9*
Apgar Score -1 minute	5.0**
Apgar Score-5 minutes	8.0**
Male Gender	107 (54%)
C-section	107 (54%)
CPAP	151 (76%)
Mechanical Ventilation	148 (74%)
Patent Ductus Arteriosus	36 (18%)
Intraventricular Hemorrhage (grade I-IV)	27 (14%)
Bronchopulmonary Dysplasia	92 (46%)
Sepsis	34 (17%)
Necrotizing Enterocolitis	13 (7%)
Dopamine	41 (21%)
Exogenous Surfactant	141 (71%)
Initial Hematocrit (%)	45.1 ± 7.5*
Length of Stay (days)	63.8 ± 27.6*

** Mean ± sd*
*** Median*

Further investigation is needed to study the strong association of length of stay with transfusion and donor number.

In addition to length of stay, prolonged mechanical ventilation was associated with transfusion and donor number in our population. Again, this finding may be secondary to higher phlebotomy requirements in preterm infants with a need for supplemental oxygen. [10] However, the exact hemoglobin and level of respiratory support at which oxygen delivery becomes compromised is unknown and can only be estimated based on unreliable clinical parameters.[13] Our finding that periventricular leukomalacia, necrotizing enterocolitis, and use of dopamine are associated with transfusion and donor number reflect the requirement for transfusion in conditions with impaired tissue oxygenation. Our data emphasize the need to target infants with these conditions for reducing donor exposure. Investigation of the relationship between oxygen supply and demand in infants with hypotension, respiratory compromise, intestinal and cerebral ischemia would aid in establishing strict guidelines for transfusing infants with these conditions.

An important part of the pathophysiology of the anemia of prematurity involves diminished response of premature infants in producing erythropoietin to a hypoxic stimulus.[8] Because of this attenuated ability to produce endogenous erythropoietin, treatment with recombinant human erythropoietin has been employed as a therapy for anemia of prematurity. [1-3] However, the population of preterm infants who would derive the greatest benefit from this therapy has yet to be elucidated. In our population of VLBW infants, birth weight and initial hematocrit were predictive of transfusion and donor number. Gestational age was not predictive after multivariate analysis. This relationship is due to close correlation of the two variables, with birth weight superseding gestational age in the multivariate models. Brown et al have previously demonstrated gestational age less than 30 weeks to be most predictive of the need for greater than two transfusions. [14] In contrast to this data which indicate that infants of the youngest gestational age receive the highest number of transfusions, previous studies have shown that recombinant human erythropoietin is most effective when administered to larger infants. [2,3] Only one double blind placebo controlled study of recombinant erythropoietin has include infants less than 750 grams. [1] Furthermore, Maier et al demonstrated that low birth weight and gestational age were most predictive of transfusion in a population of infants receiving erythropoietin.[15] Although our data indicate that recombinant human erythropoietin would have the greatest impact if offered to the smallest infants, administration of erythropoietin to extremely low birth weight infants (<1000g) may be limited by the need to supplement enteral iron and the need for frequent intramuscular injections. [16] Additional study is needed to determine how to safely and effectively administer this drug to infants of the lowest birth weight.

Anemia of prematurity has been previously classified into early and late anemia.[9] Early anemia of prematurity is associated with high phlebotomy losses. This association was emphasized in the erythropoietin trial of Shannon et al, in which infants received a mean of 3.5 transfusions prior to enrollment. [1] In our population, bronchopulmonary dysplasia and patent ductus arteriosus were predictive of donor number but not transfusion number. The need for surgical ligation of a patent ductus has previously been shown to be associated with increased blood transfusion. [14] We speculate that these factors were associated with donor number and not transfusion number in our population, because infants with these conditions continued to receive transfusions later in their hospital course at which time they are likely to be exposed to a new donor with each transfusion.

Many of the variables associated with donor and transfusion number in our investigation are not known to the clinician at the time of birth; for example, the diagnosis of bronchopulmonary dysplasia or the length of hospital stay. Although our data indicate that these factors are important

in contributing to the need for transfusion, it may be difficult to develop a treatment strategy using these variables. A more useful model may be one using variables known at birth, allowing early intervention, since the majority of transfusions occur during the early part of an infant's hospital stay. [17] The models created using only birth weight and initial hematocrit correlated well with transfusion and donor number. Therefore, these clinical variables, while not accounting for all the clinical conditions and variability associated with RBC transfusion, may be used early in an infant's hospital course to predict transfusion number, initiate interventional strategies, and counsel parents.

In conclusion, our data are the first to demonstrate an association between length of hospital stay, transfusion and donor number in a population of VLBW infants. Defining the population of infants at greatest risk provides a target for intervention. Along with erythropoietin, strict transfusion criteria, strategies to decrease phlebotomy losses, and autologous transfusion have all been proposed to decrease donor exposure in infants. Our data help to provide the ground work to identify a population of infants who would derive the greatest benefit from such interventions. Further investigation is needed in order to effectively apply these interventions to a target population.

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